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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KALLIS, RUSSELL	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 08/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/524,827	SAUER ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *19,20,33,34 and 39-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,21-32,35-38 and 47-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: attached sequence reports 1,2 &3.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-38 and new claims 47-52 in the reply filed on 5/30/2006 is acknowledged. The traversal is on the ground(s) that no evidence has been provided for breaking unity of invention. This is not found persuasive because a genetically modified organism having a modified ketolase activity comprising the amino acid sequence of SEQ ID NO: 2 does not constitute a contribution over the prior art because processes for modifying the ketolase activity of organisms and the ketolase comprising the amino acid sequence of SEQ ID NO: 2 were both known in the art (see art rejection below). Further, with respect to Applicant's arguments on page 13 of the response, it would be remiss on the part of the Examiner no to point out to Applicant that Claim 1 is not drawn to a β-ketolase as argued on page 13 but is drawn to any ketolase of which the activity has been modified in some unspecified manner. It is well known among those of skill in the art that the category of β-ketolases encompasses at least ten distinctly classified enzymes which form different products (Pokorny D. *et al.* J. of Bacteriology; Aug. 1999, pp. 5051-5059; see introduction beginning of column 1); and thus have different activities and structure-function relationships. Furthermore, Applicant's remarks that the restriction of dependent claims is incorrect because that only applies to dependent claims that are linked one after another i.e. serially and not as in the instant Application where the dependencies are nested into separate and distinct Groups (i.e. Claim 35 is not dependent from claim 33 or 34).

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-52 are pending. Claims 19-20, 33-34 and 39-46 are withdrawn. Claims 1-18, 21-32, 35-38 and 47-52 are examined.

Claim Objections

Claims 1-18, 21-32 and 35-38 are objected to because of the following informalities: the claims recite non-elected material. Appropriate correction is required.

Claim 48 is objected to because of the following informalities: the correct spelling should be Tagetes erecta as in claim 23. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1-7, 9-12, 14 and 16-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant broadly claims a process for preparing ketocarotenoids by cultivating genetically modified organisms that have a modified ketolase activity in caused by a sequence derived from SEQ ID NO: 2 by substitution, deletion, or addition and which has an identity of at least 42% to SEQ ID NO: 2; a sequence derived from SEQ ID NO: 16 by substitution, deletion, or addition and which has an identity of at least 20% to SEQ ID NO: 16; and a sequence derived from SEQ ID NO: 18 by substitution, deletion, or addition and which has an identity of at least 20% to SEQ ID NO: 18 and a genetically modified organism thereof.

Applicant describes a ketolase of SEQ ID NO: 2 encoded by SEQ ID NO: 1; a hydrolase of SEQ ID NO: 16 encoded by SEQ ID NO: 15; and a β-cyclase of SEQ ID NO: 18 encoded by SEQ ID NO: 17.

Applicant does not describe a sequence that has at least 42% sequence identity to SEQ ID NO: 2 and that causes a ketolase activity to become modified in an organism other than SEQ ID NO: 2; or a sequence that has at least 20% sequence identity to SEQ ID NO: 16 and has hydroxylase activity other than SEQ ID NO: 16; or a sequence that has at least 20% sequence identity to SEQ ID NO: 18 and has a β-cyclase activity other than SEQ ID NO: 18.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. The court stated that, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of ketolase, encoding sequences that encode ketolases having at least 42% activity to EQ ID NO: 2 or that modify ketolase activity in an organism; or nucleic acid sequences that encode either a hydroxylase having at least 20% sequence identity to SEQ ID NO: 16 or encode a β-cyclase having at least 20% sequence identity to SEQ ID NO: 18. Applicants only describe a ketolase of SEQ ID NO: 2 encoded by SEQ ID NO: 1; a hydrolase of SEQ ID NO: 16 encoded by SEQ ID NO: 15; and a β-cyclase of SEQ ID NO: 18 encoded by SEQ ID NO: 1. Furthermore, Applicants fail to describe structural features

common to members of the claimed genus of ketolases, hydroxylases or β-cyclases. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for ketolase, hydroxylase or β-cyclase activity, it remains unclear what features identify a ketolase, a hydroxylase or a β-cyclase. Since the genus of ketolases, hydroxylases or β-cyclases has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

Sequences that which are 42% to SEQ ID NO: 2 or 20% complementary to SEQ ID NO: 16 or 18 encompass naturally occurring allelic variants, mutants of SEQ ID NO: 2, 16 and 18, as well as sequences encoding proteins having no known ketolase, hydroxylase or β-cyclase activity, of which Applicant is not in possession. Accordingly, the specification fails to provide an adequate written description to support the genus of ketolases, hydroxylases or β-cyclases encompassed by the percent identity language as set forth in the claims. (See Written Description guidelines published in Federal Register/Vol. 66, No.4/Friday, January 5, 2001/Notices: p.1099-1111).

Claims 1-7, 9-12, 14, 16-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process drawn to preparing ketocarotenoids caused by modifying or increasing the activity of a ketolase, hydroxylase and a β-cyclase caused by of SEQ ID NO: 2 encoded by SEQ ID NO: 1; a hydroxylase of SEQ ID NO: 16 encoded by SEQ ID NO: 15; and a β-cyclase of SEQ ID NO: 18 encoded by SEQ ID NO: 17, does not reasonably provide enablement for a process drawn to preparing ketocarotenoids caused by modifying or increasing the activity of a sequence that has at least 42% sequence identity to SEQ ID NO: 2 and that

causes a ketolase activity to become modified in an organism other than with SEQ ID NO: 2; or a sequence that has at least 20% sequence identity to SEQ ID NO: 16 and has hydroxylase activity other than with SEQ ID NO: 16; or a sequence that has at least 20% sequence identity to SEQ ID NO: 18 and has a β-cyclase activity other than with SEQ ID NO: 18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

Applicant broadly claims a process for preparing ketocarotenoids by cultivating genetically modified organisms that have a modified ketolase activity in caused by a sequence derived from SEQ ID NO: 2 by substitution, deletion, or addition and which has an identity of at least 42% to SEQ ID NO: 2; a sequence derived from SEQ ID NO: 16 by substitution, deletion, or addition and which has an identity of at least 20% to SEQ ID NO: 16; and a sequence derived from SEQ ID NO: 18 by substitution, deletion, or addition and which has an identity of at least 20% to SEQ ID NO: 18 and a genetically modified organism thereof.

Applicants provide guidance for constructing vectors comprising SEQ ID NO: 1, 15 and 17 and transformation of Marigold therewith.

Applicants do not teach process of preparing ketocarotenoids in any organism or plant using sequences derived from SEQ ID NO: 2 by substitution, deletion, or addition and which has an identity of at least 42% to SEQ ID NO: 2; a sequence derived from SEQ ID NO: 16 by substitution, deletion, or addition and which has an identity of at least 20% to SEQ ID NO: 16; and a sequence derived from SEQ ID NO: 18 by substitution, deletion, or addition and which has an identity of at least 20% to SEQ ID NO: 18 and a genetically modified organism thereof.

The state-of-the-art is such that one of skill in the art cannot predict that the specific activity in an enzyme having unspecified amino acid substitutions to at least 58% of the primary sequence and maintaining ketolase activity or unspecified amino acid substitutions to at least 80% of the primary sequence and maintaining cyclase or hydroxylase activity. For example the tomato lycopene beta-cyclase polypeptide has been shown to have at least 36% sequence identity to the lycopene epsilon-cyclase from tomato (Ronen G. *et al.* The Plant Journal, 1999; Vol. 17, No. 4, pp. 341-351), and thus a polypeptide sequence having an identity of 20% to a beta cyclase of SEQ ID NO: 18 would not retrieve a beta cyclase but an epsilon cyclase.

Given the lack of guidance in the instant specification, undue trial and error experimentation would be required for one of ordinary skill in the art to make a myriad of substitutions to the polypeptide in some unspecified manner and test for activity *in vivo* or *in vitro*.

Therefore, given the breadth of the claims; the lack of guidance and working examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation

would be required to practice the claimed invention, and therefore the invention is not enabled throughout the broad scope of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-18, 21-32, 35-38 and 47-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,232,530 issued 15th of May 2001 in view of Shewmaker *et al.* WO 99/07867 published 18th of February 1999 and in further view of Applicant's specification.

The claims are broadly drawn to a process for preparing ketocarotenoids by cultivating genetically modified organisms that have a modified ketolase activity caused by a sequence derived from SEQ ID NO: 2 by substitution, deletion, or addition and which has an identity of at least 42% to SEQ ID NO: 2; a sequence derived from SEQ ID NO: 16 by substitution, deletion, or addition and which has an identity of at least 20% to SEQ ID NO: 16; and a sequence derived from SEQ ID NO: 18 by substitution, deletion, or addition and which has an identity of at least 20% to SEQ ID NO: 18 and a genetically modified organism thereof.

U.S. Patent 6,232,530 teaches marigold transformed with SEQ ID NO: 18 and a beta-hydroxylase (*crtZ*) using a petal specific promoter for the production of selected carotenoids in Mariglod flower petals (see column 5 lines 10-27 and lines 53-57; columns 17-20; attached sequence report 3, and the claims).

Shewmaker teaches a method for increasing or altering carotenoid composition toward increasing the accumulation of higher levels of beta-carotene derived carotenoids, such as zeaxanthin, canthaxanthin and astaxanthin by heterologous expression of lycopene beta-cyclase and *crtW* (ketolase) and *crtZ* (hydroxylase) (see page 12 line 22 to page 13 line 26; and page 47 and claim 19) in a plant.

Applicant's specification teaches SEQ ID NO: 2, SEQ ID NO: 16 and SEQ ID NO: 18 were known in the art prior to Applicant's filing (see specification page 1 line 32 and page 2 lines 4-6, and attached sequence reports).

It would have been obvious at the time of Applicant's invention to further modify the invention of U.S. Patent 6,232,530 to substitute a *crtZ* encoding a hydroxylase of SEQ ID NO: 16 and to further include a *crtW* encoding a ketolase of SEQ ID NO: 2 to prepare ketocarotenoids in transformed Marigold and plants in general. One of ordinary skill in the art would have been motivated by the success of both U.S. Patent 6,232,530 and Shewmaker that ketocarotenoid production in transformed marigold and transformed plants in general are valuable in the art and that SEQ ID NO: 2, 16 and 18 were available in the art and could be interchanged with other cyclase, ketolase and hydroxylase encoding polynucleotides; and would have a reasonable expectation of success of engineering ketocarotenoid production in transformed plants and Marigold given the success of both Shewmaker and U.S. Patent 6,232,530.

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Russell Kallis Ph.D.
August 4, 2006

RUSSELL P. KALLIS, PH.D.
PRIMARY EXAMINER

Russell Kallis